
بسم الله الرحمن الرحيم

AETIOLOGY OF ORAL CANCER

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What is oral cancer?

- Oral cancer is **cancer found in the oral cavity** (e.g. lips, labial & buccal mucosa ,floor of the mouth soft palate , tongue)
- The soft tissues of the oral cavity are **covered by stratified squamous epithelium**
- **90% of these cancers are squamous cell carcinoma**

- The **primary function** of oral epithelium is the **protection** of the underlying tissue against fluid loss and against the ***ingress*** **of potentially harmful environmental agents**
- These include microbial toxins , enzymes and ***carcinogens*** from foods and beverages

- The **integrity** of oral mucosa is maintained by ***cell production*** in the deeper layers **balanced** by ***loss of cells*** from the surface { i.e. proliferation of cells must be compensated by cell death. }

- All living things depend on **genes** to hold the information to build and **maintain their cells**

- **A gene is a portion of DNA** that contains **" sequences "** that determine **what** the gene does and **when** the gene is active (expressed). When a gene is active, sequences are copied in a process called transcription

- **DNA is a nucleic acid** that contains the genetic instructions
- Genes make up **Chromosomes**

Definition

- **Cancer** may be defined as **uncontrolled tissue growth** in **susceptible** patients , which results from an ***imbalance*** between **cell division** and **programmed cell death** {**apoptosis**}

Incidence:

- Oral cancer accounts for about 5% of all cancers in the united states, 1-2% in the UK and about 40% in India, Srilanka , Sudan

- These differences are due to:

I. Differing population habits > where the habit of tobacco or snuff chewing is wide spread

II. lack of preventive education

III. The quality of medical records in various countries.

Age, sex and Race:

- As with so many carcinomas, the risk of intra oral cancer *increases with increasing age*, especially for males.
- This suggests that any carcinogen have to act over a *long period.*
- *White men*, have a higher risk after 65 years of age than do any other group
- Females, whether white or non-white, have a much lower incidence than males at all age levels. The overall *male to female ratio is 3: 1.*

Cancer is a genetic disease

- Cancer forms when genes within a normal cell are **damaged & mutated**
- Mutations occur in certain ***key genes***
- These key genes can be grouped into **three classes**

Key genes

- **Proto-Oncogenes :** Growth ***promoting genes*** that norm the cell when to grow and divide { i.e. regulates cell growth differentiation}
- **Anti-oncogenes {Tumor suppressor genes }:** Grow ***inhibition genes*** whose normal function is to maintain the cell in a non- c state
- **DNA repair genes** whose function is to ***repair*** damage t

- A **proto-oncogene** may be transformed into **activated oncogene** due to **mutations** through the action of *viruses* , *irradiation* or *chemical carcinogens*

- Once **oncogenes are activated** they stimulate the production of excessive amount of **new genetic material** through overexpression of the involved gene

- **An activated oncogene** is a gene ,which participates in the onset and ***development of cancer***

- When a **tumor suppressor gene** { **anti-oncogene** } is **mutated** it becomes **inactive** causing loss or reduction in its function, the cell can ***progress to cancer***

How key genes become defective?

- The answer to the question is very often difficult to address
- ***No single*** recognizable cause has been found for oral cancer
- It is likely that **many factors** are involved in the etiology ,and these vary in different groups

1. **Therefore** , oral cancer is a **multifactorial disease**
2. **It is multistep process involving multiple sequential *mutations* which accumulate within the cell**

Theory of carcinogenesis

- The **two-stage theory** of carcinogenesis , suggests that carcinogenesis involves an initiation stage followed some time later by a promotion stage
- **Initiation stage** requires **exposure** to a specific carcinogenic agent
- **Promotion stage** occur either by **continued** exposure to the specific agent or to non-specific irritants

Etiological factors:

- Nearly all cancers are caused by **abnormalities in** the **genetic material**
- These abnormalities may be due to the effect of **carcinogens** such as tobacco smoke , alcohol , chemicals
- Multiple ***factors*** appears to be involved in most human cancer. Some factors may have
  - **A direct local** { ***extrinsic*** } effect on tissues {*e.g. tobacco & sun light*},
  - Whilst others may cause **systemic** {***intrinsic***}**disturbances** {*iron deficiency*}which render the host more **susceptible** to the effect of carcinogens

Etiological factors:

- **Carcinogenesis**, probably involves **interplay** between these *extrinsic* and *intrinsic* factors and their interaction may have **complimentary** effects

The main extrinsic and intrinsic factors involved in the etiology of oral cancer are:

1-Tobacco

2-alcohol

3-diet and nutritional dificiency

4-radiation and ultraviolet rays

5-infectious agents

6-dental factors

7-immunosuppression

8-occupation

9-precancerous

1.Tobacco

Primary risk factor for oral cancer in all forms

1.Tobacco

- Tobacco is regarded as the most important factor for developing oral cancer
- Approximately 75% of oral cancers are attributed to the use of smoked and smokeless tobacco
- Tobacco is a *chronic irritant* that can cause damage to the cells of the oral mucosa

- The rate increases with the amount smoked or chewed and the duration of use.
- The method of smoking may influence the relative risk of oral cancer

A) Smoking tobacco {cigarettes cigars , pipe }

- **Cigarette smoke** contains about 4,000 chemical agents, including more than **60 carcinogens** (e.g., carbon monoxide, tar, arsenic, lead)
- The same **carcinogens** found in cigarette smoke are also found in pipe and cigar smoke.
- **Smoke** and **heat** from cigarettes, cigars, and pipes irritate the mucous membranes of the mouth.

A) Smoking tobacco {cigarettes cigars pipe }

- **Cigar** and **pipe** smoking are linked to a **greater risk** for the development of oral cancer than that of cigarette smoking
- Cigar smokers who inhale deeply are six times more likely to develop oral cancer

- Pipe smokers have an especially ***high risk*** for lip **cancer because of the *static contact*** of the pipe stem with the lower lip

- Pipe smoking is also , associated with nicotinic stomatitis ,a white lesion of the palate, arising due to pipe fumes
- It is a reversible condition , of no premalignant potentiality , if the habit is ceased

B)reverse smoking

- :The habit of holding the lighted end of the cigarette inside the mouth
- A habit that is particularly common in women
- Wide spread in **India** , **South America** and various other countries
- Results in a high incidence of ***palatal carcinoma*** one of the rarest site for oral cancer
- Due to a high concentration of the ***carcinogen*** ***striking*** **the palatal surface** in a ***focal area***

C) Smokeless tobacco

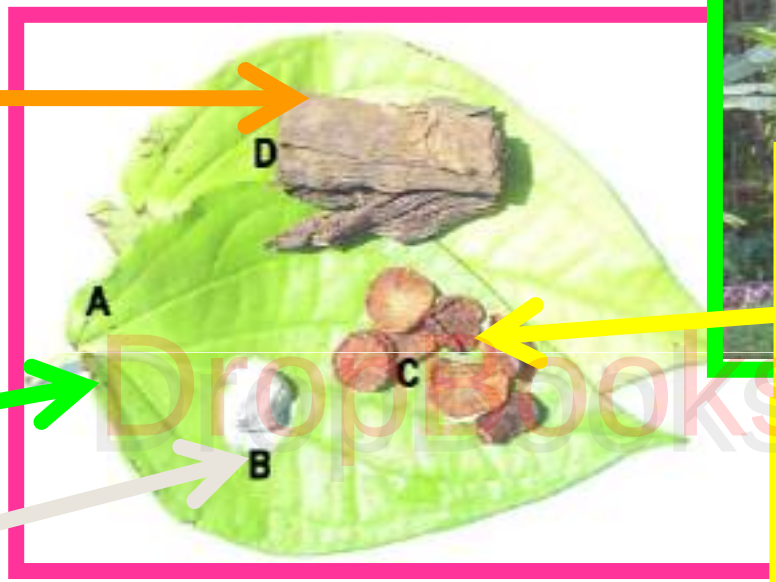
1.Snuff tobacco

- Snuff is finely ground or ***powdered tobacco*** which may be **inhaled dry** or used **moist** {**snuff-dipping**} by placing a pinch of snuff between the gum and the cheek or the upper lip for a prolonged period
- This result in **hyperkeratotic** lesions of the gingiva and buccal mucosa and associated with a significantly increased ***risk for carcinoma***

C) Smokeless tobacco

2.Betel quid (pan) chewing habit

- Consists of
  - Tobacco
  - Areca nut
  - wrapped **in** betel leaf
  - lime
  - other **spices** are according to custom and individual ta



C) Smokeless tobacco

2.Betel quid (pan) chewing habit

- This combination of ingredients is more **carcinogenic** than tobacco alone
- The slake **lime** **enhances absorption** of molecules from other products
- Pan is normally chewed after meals its effect being to aids *digestion* ,to produce slight *euphoric* effect
- It is ***kept in the mouth*** for a long time , habitual users may have a pan 24 hours a day

C) Smokeless tobacco

- Use of ***chewing tobacco*** or ***snuff*** causes irritation from ***direct contact*** with the mucous membranes
- This habit induces **leukoplakia** and **malignant** transformation **where** pan is held in the mouth
- ***Factors*** like **alcohol** , **trauma** , **candida albican** infection and **nutritional deficiencies** may **contribute to the development of malignant change**

2 Alcohol

- **Second major** factor in the development of oral cancer
- **Identification** of alcohol alone as a carcinogenic factor has proved to be difficult because of combination of smoking and drinking habits by most oral cancer patients
- Alcohol is regarded as ***promoter***, if ***not initiator***

2 Alcohol

The effect of alcohol occur through :

1. **Its** ability *to* ***irritate*** the mucosa
2. **Its** ability to act as a ***solvent*** for carcinogens [specially tobacco]
3. **Contaminants** and **additives** with **carcinogenic potential** that are found in alcoholic drinks have a role in oral cancer development

2 Alcohol

4. **Alcohol** could act **intrinsically** through **systemic** mechanism via liver damage or cirrhosis

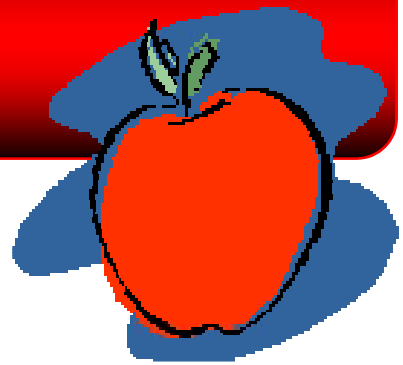
- Impaired metabolism and
- Nutritional deficiencies could damage the ability of the oral mucosa to maintain its barrier function.

- **Histological** studies revealed ***atrophy*** of oral mucosa

- **The effect of *alcohol* and *tobacco* is multiplicative**

N.B The risk is *dose* and *time* dependent

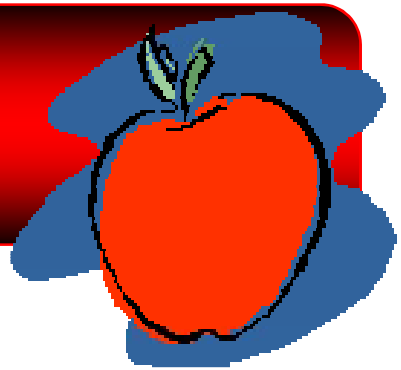
3-Diet and Nutrition



❖ **Nutritional deficiencies**

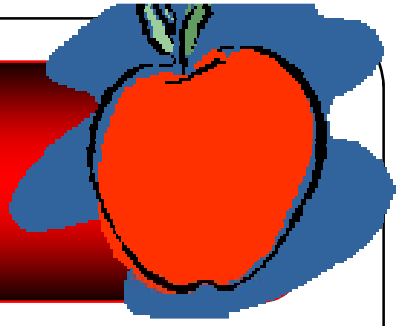
1. **Iron deficiency (Plummer Vinson syndrome)**
2. **Vitamin A deficiency.**
3. **Vitamin C and Vitamin E deficiency (Antioxidants)**

Iron deficiency



- **Iron** is essential to the normal functioning of epithelial cells
- In deficiency states , these epithelial cells turn over more rapidly and produce an ***atrophic mucosa*** { become more susceptible to chemical *carcinogens* }

Iron deficiency



- **Plummer-vinson {Paterson Kelly}** syndromes a severe form of **iron** – ***deficiency anemia***
  - Affects middle-aged females
  - Manifested by painful **red** tongue , ***epithelial atrophy*** and ***dysphagia***
  - Associated with high frequency of **oral squamous cell carcinoma**

Vitamin A

❖ ***Vitamin A*** is essential to maintain intact epithelial tissues as a physical barrier to infection { i.e. for the correct functioning of epithelial cells}

Vitamin A

- It has been suggested that vitamin A has a ***protective*** *role* in oral precancer and cancer

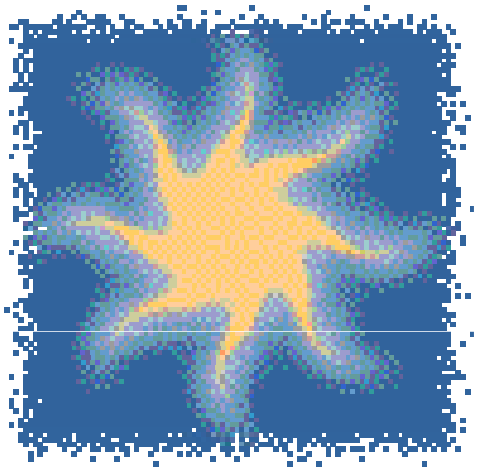
- Long term therapy with ***Retinoic acid*** {acidified form of Vitamin A} and ***Beta Carotene*** showed regression of some leukoplakic lesions and reduction in the severity of dysplasia

Vitamin C , Vitamin E &Beta Caroten {antioxidant}

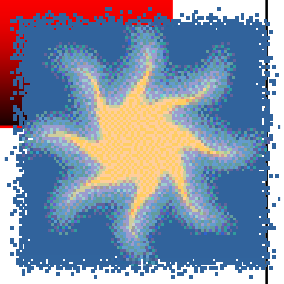
- **A high intake of antioxidants has been recently shown to exerts a *protective* influence against many types of cancer**

4-Radiation and ultra violet rays

- **Sun (ultra violet rays)**
- **X-irradiation**



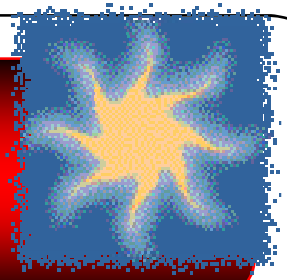
Sun {ultra violet rays}



- ***Ultraviolet*** light is a **carcinogenic agent**

- Long term or excessive exposure to ultraviolet radiation results in ***Actinic Cheilosis***
  - A diffuse premalignant alteration of the ***lower lip***

Sun {ultra violet rays}



- **Outdoor workers** such as farmers and fishermen are more liable to develop lip and skin cancer
- Confined predominantly to **fair skinned** people
- **Rare in dark skinned** races because of the protection conferred against ultraviolet light by **melanin** pigment

➢ **i.e**. The ***cumulative*** dosage of sun light and the amount of protection by ***natural pigmentation*** are of great significance in the development of skin cancer of the lip

radiotherapy

- It decreases the **immune reactivity**
- It produces **abnormalities** in the **chromosomal** material

radiotherapy

- Radiotherapy **to the head and neck** increase the risk of the later development of a ***new*** primary oral malignancy, either carcinoma or sarcoma
- The effect is **dose-dependant** ,but even low dose radiotherapy for benign lesions may increase the local risk

- **However**, the small amount of radiation from routine diagnostic **dental radiograph** **has not** been associated with oral mucosal carcinoma

5-Infectious agents

- **Viral. (HPV-HSV-HIV-Epstien Barr virus**
- **Bacterial (syphilis) → tongue lesion (3ry stage).**
- **Fungal, (chronic candidiasis)**

Oncogenic viruses

- Oncogenic viruses [tumor- producing] play a **major role** in a variety of cancers ,
- Although ***no*** virus has definitively been proven to cause oral cancer

Oncogenic viruses

- **Epstein-Barr virus** causes **Burkitt' s** lymphoma and nasopharyngeal carcinoma
- **Hepatitis B and C viruses** cause carcinoma of liver
- **HIV** patients have an increased incidence of **kaposi' s** sarcoma

Herpes simplex viruses

- **HSV** ,specially type 2 ,has been confirmed to cause cancer of the uterine cervix

- It has been suggested as an etiologic factor in oral carcinoma

Human papillomavirus

- HPV are wide spread in normal epithelium so it is difficult to establish a causative role in oral cancer but they may act *in concert with other factors*, such as smoking and alcohol

- HPV 16,18, subtypes have been **detected** ***in*** *oral carcinoma*

- HPV results in carcinoma of the genitourinary tract

Bacterial agent

- **Syphilis** has been thought to have a strong association with the development of **tongue carcinoma**
- It has been found that tongue carcinomas were ***due to*** the effect of ***arsenical compounds*** used to treat syphilis
- With the advent of antibiotics ,late {tertiary}stage of syphilis is now rare

Chronic candidiasis

- Chronic candidal infection is often associated with speckled leukoplakia
- Such lesions are more likely to undergo malignant transformation
- It has been suggested that fungus is responsible for this transformation, the ***hyphae*** *interfere* with the cell metabolism,resulting in **dysplastic** change

6-Dental factors

- **Oral cancer is most common in neglected mouth**
- **Mechanical trauma from ill fitting denture ,broken fillings sharp edges of teeth have been *incriminated* in the etiology of oral cancer**
- **Chronic irritation is regarded as *promotor* rather than an initiator of oral cancer**

7-Immunosuppression:

- Increased risk of oral cancer in patients following renal transplantation , those patients are under immunosuppressive therapy , newly created **malignant cells can not be** recognized and **destroyed** at an early stage

- Increased risk of oral cancer in patients with AIDS

8-Occupation:

- High incidence of oral carcinoma has been reported in **textile workers** particularly those exposed dust from raw cotton and wool

- Increased risk of oral carcinoma among workers in the **printing trades**


Thank you